Biol Blood Marrow Transplant 22 (2016) 796–801

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Reviews

Evolution of Hematopoietic Cell Transplantation for Immunoglobulin Light Chain Amyloidosis

Taimur Sher*, Angela Dispenzieri, Morie A. Gertz

Department of Medicine, Mayo Clinic, Jacksonville, Florida

Article history:
Received 29 June 2015
Accepted 8 October 2015

Key Words:
Immunoglobulin light chain amyloidosis
AL amyloidosis
Stem cell transplantation
Hematopoeitic stem cell transplantation

A B S T R A C T

Immunoglobulin light chain amyloidosis is the most common type of systemic amyloidosis. Hematopoietic stem cell transplantation (HCT) is an effective treatment option for AL however due to multi-organ involvement in this disease HCT is feasible in a minority of patients. To maximize the benefit and minimize toxicity it is of paramount importance to optimize the selection of patients for HCT. In this review we discuss evolution of HCT and its typical application to a case of AL amyloidosis.

CASE SUMMARY

A 45-year-old male presented to our institution for management of recent diagnosis of lambda light chain amyloidosis (AL) established on a kidney biopsy that was done to evaluate new-onset nephrotic syndrome. The patient was previously healthy and had no major chronic medical comorbidities. The work-up demonstrated lambda light chain plasma cell dyscrasia (serum lambda light chains: 32 mg/dL with abnormal kappa: lambda; 8% lambda restricted marrow plasmacytosis with perivascular congophilic deposits), normal hepatic and renal function, and normal echocardiogram, N-terminal of the pro-hormone of beta natriuretic peptide (NT-ProBNP), and cardiac troponin-T (cTNT). After a complete review of the case, the patient was diagnosed with systemic immunoglobulin AL of the lambda light chain type with renal involvement and we had a detailed discussion about possible treatment options.

DISCUSSION

Immunoglobulin light chain is the most common form of systemic amyloidosis, characterized by extracellular deposition of amyloidogenic light chain fragments that result in progressive organ dysfunction. With a median survival of 12 to 17 months, AL is a fatal disease [1]. Death results from rapid clinical deterioration due to the involvement of heart, kidneys, liver, and the gastrointestinal tract. Antineoplastic therapy aimed at eradicating the underlying transformed plasma cells, the source of amyloidogenic light chains, and organ-directed supportive care are the mainstays of treatment in AL. Antiplasma cell therapy in AL involves standard-dose therapy or high-dose myeloablative therapy as part of autologous hematopoietic cell transplantation (HCT). In this review we focus on the evolution of the role of HCT in AL, the unique challenges it poses in the management of AL patients, and its evolving role in the era of new treatment modalities.

A Historical Perspective

Melphalan given orally in combination with steroids such as dexamethasone (MelDex) demonstrated significant activity in AL in early clinical investigations. This combination delivered high hematologic response rates, including complete remission rates that exceeded those in multiple myeloma and also resulted in improved organ function and survival of AL patients [2]. The therapeutic benefit from MelDex and other steroid combinations required prolonged treatment over the course of 12 to 18 months. This long-term use has been associated with a high incidence of secondary myeloid malignancies (up to 20%) and other metabolic and cardiovascular toxicities associated with chronic steroid use in this sick patient population [3]. The success of HCT in multiple myeloma in the 1980s established high-dose melphalan as the standard of care, as it resulted in improved response rates and survival and also provided a

Financial disclosure: See Acknowledgments on page 801.

* Correspondence and reprint requests: Taimur Sher, MD, Division of Hematology and Medical Oncology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL, 32224

E-mail address: Sher.taimur@mayo.edu (T. Sher).

http://dx.doi.org/10.1016/j.bbmt.2015.10.010
1083-8791/

potential treatment-free interval to the myeloma patients, obviating the need for continued therapy. Therefore, it was logical to explore HCT in AL; however, organ dysfunction and rapid clinical deterioration in these patients presented a formidable barrier and it was not until the mid-1990s that the first experience with this modality was reported in AL [4]. The role and practice of HCT in AL has considerably evolved over last 2 decades and it has become a safe and effective option for these patients primarily as a result of better patient selection.

Feasibility of HCT in AL

The earliest experience with HCT was reported in a select group of 25 AL patients with a median age of 48 (range, 29 to 60) years. At a median follow-up of 2 years, 68% of the patients were alive with an early transplantation-related mortality (TRM) of 20% [5]. Hematological complete response, by criteria predating the immunoglobulin light chain assay, was achieved in 60% of patients. Over the subsequent 5 to 6 years, several groups reported their experience. Using a melphalan dose ranging between 100 mg/m^2 and 200 mg/m^2, these series demonstrated that high-dose melphalan was associated with higher hematologic response rates, including complete remissions, in up to 40% of patients and organ responses in up to 45% [6,7]. As a result of this experience, the ability of HCT to effectively target the neoplastic plasma cells in AL was firmly established. However, an important lesson learned from these studies was that there is unacceptably high TRM of 10% to 43% at 3 months [7]. The primary cause of mortality was sudden cardiac death, gastrointestinal hemorrhage, hypotension, and sepsis with multiorgan failure. Another key challenge of that era was the lack of consistent and sensitive markers of response to treatment and predictors of mortality that could inform patient selection and prognostication early in the disease course. High mortality, with unique and severe morbidities, defined HCT for AL as a completely distinct entity as compared to that for multiple myeloma and other lymphoid malignancies.

These experiences led the Intergroupe Francophone du Myélome to conduct 1 of the most important studies in AL therapeutics that, to date, remains the only randomized study comparing HCT to the standard of care oral MelDex regimen in 100 AL patients. Compared with MelDex, there was no difference in the hematological and organ response rates in HCT and MelDex arms (66% versus 68% and 39% versus 45%, respectively). On intention-to-treat analysis, patients in the MelDex arm survived much longer than HCT patients (56.9 months versus 22.2 months) [8]. The TRM of HCT was 24%. There are several flaws in this study that limit its generalizability to current practice. Enrollment of patients with advanced cardiac disease, high rate of drop off, even before HDT, and absence of a clear selection basis for melphalan dosing limit the conclusions that can be made about the role of HDT in AL from this study.

Improved Safety of HCT

During the mid to late 2000s, significant progress was made to address the critical issues of high mortality and morbidly of HCT in AL. Several patient, disease, and treatment-related factors that could predict high TRM and morbidity were identified (Table 1, Figure 1) [9].

Careful patient selection has contributed to remarkable improvement in the safety of HCT. In a large series of 422 AL patients treated with HCT at Mayo Clinic, we noted a 40% reduction in TRM in patients undergoing high-dose therapy after January 2006 when compared with that of patients treated earlier (day 100 mortality of 7% versus 12%) [10]. Similarly, in a large series of 522 patients who underwent HCT at Boston University Medical Center, the investigators reported successive improvement in day 100 mortality in the second decade (4% versus 17%) [11].

Table 1
Guidelines for Patient Selection for Stem Cell Transplantation

Suggested Requirement
"Physiologic" age less than 70
Creatinine clearance >30 mL/min
cTNT < .06 ng/mL
Systolic blood pressure ≥ 90
NYHA class I/II

NYHA indicates New York Heart Association.

One of the major advancements in the management of AL during this era was the development of the 3-tiered Mayo staging system (MSS), based on the serum levels of readily available biomarkers of myocardial injury and stress, the cTNT and NT-ProBNP [12]. This staging system provided, for the first time, a reproducible and quantifiable framework that could prognosticate the outcomes of AL patients both in the HCT and nontransplantation setting. In 434 AL patients who underwent HCT at Mayo Clinic between 1996 and 2010, the MSS emerged as 1 of the most important determinants of outcome, with the median survival for stages 1 and 2 not reached at the time of data cutoff and 5.8 months for stage 3 disease [13]. In addition to being prognostic, the MSS proved instrumental in comparing patients across different studies and became an influential tool in selecting patients not only for HCT but also as an important inclusion and exclusion criteria in next generation of clinical trials. The introduction of serum free light chain assay proved indispensable in defining the hematologic response to treatment. Several studies confirmed hematologic response as the most important determinant of overall outcome and subsequent organ response [14]. In the Mayo Clinic series, the median survivals of patients with no response, partial hematologic response, or complete hematologic response to HCT were 32 months, 107 months, and not reached, respectively [13]. Investigators at Boston University reported an impressive

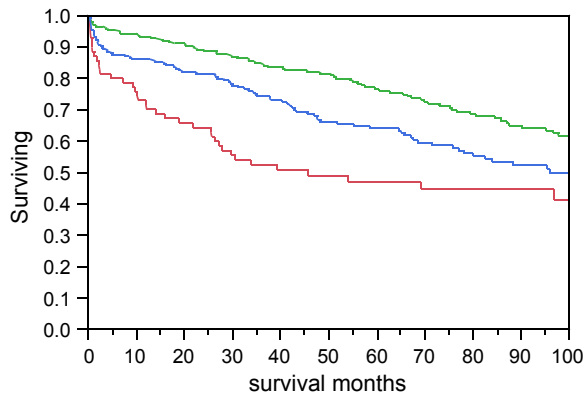

Figure 1. Overall survival in 587 AL patients treated with HCT at Mayo Clinic according to the number of involved organs: red ≥ 2 (n = 71), blue = 2 (n = 227), green = 1 (n = 288) $P < .0001$. (This Figure is available in color online at www.bbmt.org).